

I hope everyone is doing well and had a wonderful weekend.

Under Covid-19 News I report on the ACIP meeting yesterday. The second topic is an interesting comparison between the UK and US in vaccinations and deaths of persons >65.

Under Journal Review lots to share. First, an article that uses a data driven model, the researchers considered migration data between counties, the observed case numbers, and estimates of infections based on the number of people who test positive for SARS-CoV-2 antibodies. This study was done before Delta. In the next article the authors analyzed more than 40,000 coronavirus infections in UK and add to evidence suggesting that Delta may cause more severe illness than other variants with higher hospitalization rates. The next article is a prepublication article from Israel on impact of a third dose (booster). Next is an interesting article on an outbreak in elementary school with the Delta variant. The last article compares the antibody response between the Pfizer vaccine and the Moderna vaccine.

Stay safe

Ed

COVID-19 News

CDC Panel Unanimously Backs Pfizer Vax, Fortifying FDA Approval

August 30, 2021

All 14 members of the ACIP voted 'yes' to recommend the vaccine for Americans ages 16 and up. The vaccine was fully approved by the FDA last week. The vaccine is still available to teens ages 12 to 15 under an emergency use authorization from the FDA.

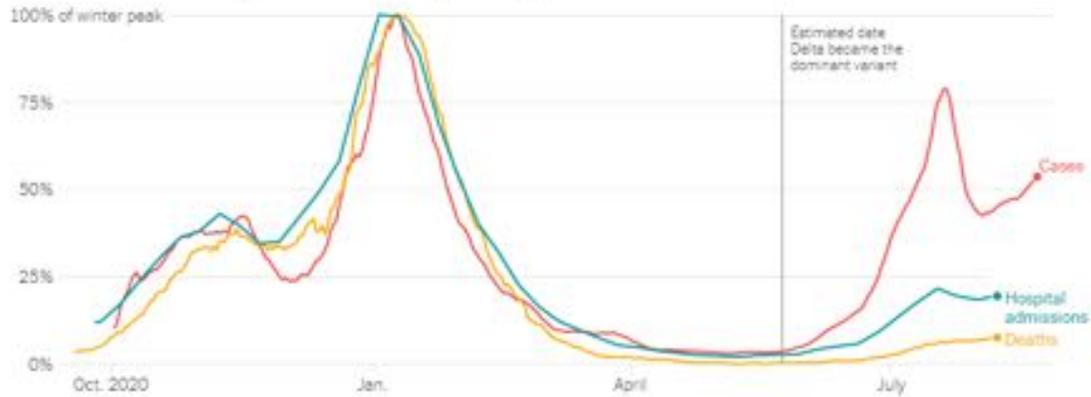
The ACIP review found the Pfizer vaccine prevented a COVID infection with symptoms about 90%-92% of the time, at least for the first 4 months after the second shot. Protection against hospitalization and death was even higher. The vaccine was about 89% effective at preventing a COVID infection without symptoms, according to a pooled estimate of five studies. The data included in the review was only updated through March 13, 2021 and does not reflect the impact of further waning of immunity or the impact of the Delta variant.

The rate of anaphylaxis, was around five cases for every million shots given. Cases of myocarditis and pericarditis were more common after getting a Pfizer vaccine than would be expected to happen naturally in the general population, but the risk was still very rare, and elevated primarily for men younger than age 30. The average hospital stay for a myocarditis case is 1 to 2 days. So far, no one in the US diagnosed with myocarditis after vaccination has died. The risk of myocarditis after a COVID infection was 6 to 34 times higher than the risk after receiving an mRNA vaccine. [See Briefing August 27, 2021]

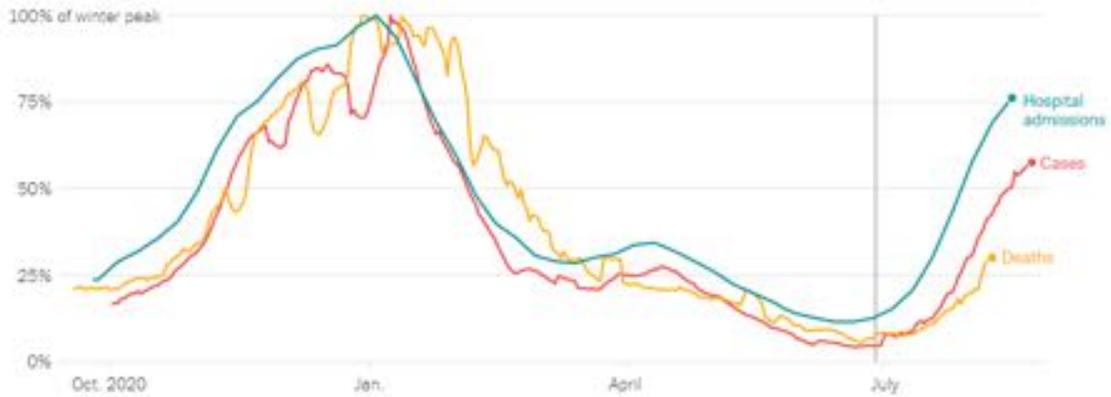
Many Older Americans Still Aren't Vaccinated, Making the Delta Wave Deadlier

NY Times August 27, 2021

Cases in the **U.K.** reached 80% of the winter peak this summer, but Covid-19 deaths and hospitalizations rose only modestly.



But in the **United States**, Covid-19 deaths are rising more quickly, and hospital admissions have already reached 75% of the winter peak.



Comment: In general, the US has done a pretty good job in vaccinating persons >65; however, we still have pockets where vaccinations rates are inadequate in persons >age 65 leading to a higher deaths.

Journal Review

Burden and Characteristics of COVID-19 in the United States During 2020

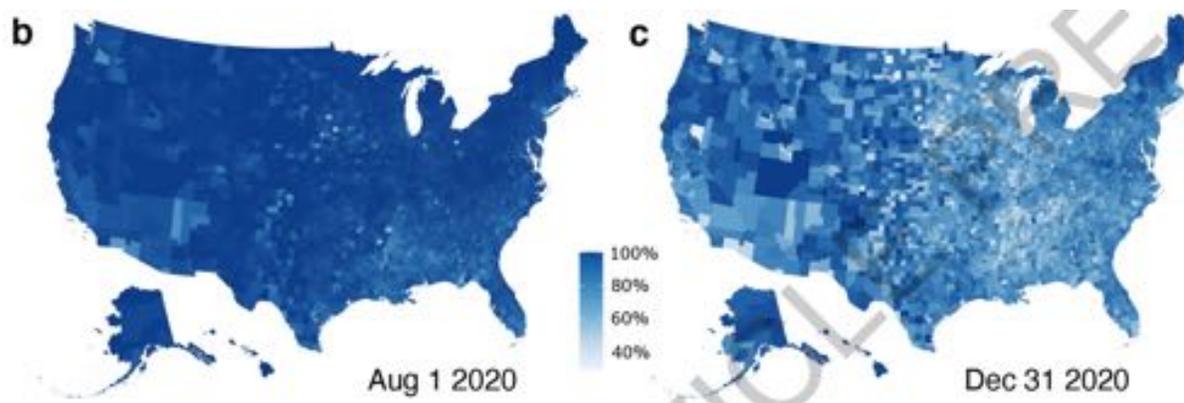
Nature published online August 26, 2021

doi.org/10.1038/s41586-021-03914-4

Using a data driven model, the researchers considered migration data between counties, the observed case numbers, and estimates of infections based on the number of people who test positive for SARS-CoV-2 antibodies.

The United States had the highest number of confirmed COVID-19 cases and deaths in the world during 2020. More than 19.6 million cases were reported by the end of the year. But the authors point out that ~70% of the population remained susceptible to viral infection. The researchers also studied the ascertainment rate, or the ratio of detected cases to the number of confirmed cases. Nationally, that value increased from 11.3% in March 2020 to 24.5% in December 2020. About one third of the US population had been infected with SARS-CoV-2 by the end of 2020. The infection fatality rate, however, decreased to 0.3% by year's end.

Estimates of population susceptibility



Comment: Their model does not represent re-infection, either through waning immunity or immune escape; however, re-infection has been documented and with the emergence of the Delta variant we are seeing record rates, vaccination breakthroughs, and hospitalizations. To date only ~172 million persons in the US are fully immunized. On a positive note, children ages 12-17 are up to 50% vaccinated. Delta's R_0 is estimated at 6-8. Based on that number we will need ~85-90% immunity to suppress community spread.

Hospital Admission and Emergency Care Attendance Risk for SARS-CoV-2 Delta (B.1.617.2) Compared with Alpha (B.1.1.7) Variants of Concern: A Cohort Study

Lancet Infect Dis published online August 27, 2021

[doi.org/10.1016/S1473-3099\(21\)00475-8](https://doi.org/10.1016/S1473-3099(21)00475-8)

The investigators did an analysis of more than 40,000 coronavirus infections in England. It adds to evidence suggesting that Delta may cause more severe illness than other variants do. Fewer than 2

percent of the infections occurred in fully vaccinated people, and there was not enough data to draw firm conclusions about hospitalization risks in that group specifically.

In this new study, researchers analyzed the health data of people who tested positive for the virus in England between March 29 and May 23, as Delta was spreading through the country. Seventy-four percent of people were unvaccinated, 24.2 percent were partially vaccinated, and 1.8 percent were fully vaccinated. Genetic sequencing confirmed that 80 percent of the study participants had been infected with the Alpha variant, while 20 percent had been infected with Delta.

For both groups, the risk of hospitalization was small, the researchers found. Just 2.2 percent of people with Alpha and 2.3 percent of those with Delta were admitted to the hospital within two weeks of testing positive for the virus. But people infected with the Delta variant were younger, on average. [This is what we are seeing in the US] When the researchers adjusted for age and other factors that are known to affect disease severity, they found that when Delta caused the infection, the overall risk of being hospitalized was more than two times as high.

When the researchers broke down the data by vaccination status, they confirmed that Delta doubled the risk of hospitalization for those who were unvaccinated or had received their first dose less than three weeks prior. The fully vaccinated group was too small to be rigorously analyzed on its own, the researchers said.

	Alpha variant (B.1.1.7)	Delta variant (B.1.617.2)	HR (95% CI), delta variant vs alpha variant	
			Unadjusted	Adjusted*
Hospital admission within 14 days after specimen	764/34 656 (2.2%)	196/8682 (2.3%)	1.03 (0.88-1.21)	2.26 (1.32-3.89)
Hospital admission or emergency care attendance within 14 days after specimen	1448/34 656 (4.2%)	498/8682 (5.7%)	1.39 (1.25-1.53)	1.45 (1.08-1.95)

Comment: This analysis of more than 40,000 coronavirus infections in UK adds to evidence suggesting that Delta may cause more severe illness than other variants do. Results suggest that outbreaks of the delta variant in unvaccinated populations might lead to a greater burden on health-care services than the alpha variant. This study helps explain the current situation in the US.

BNT162b2 Vaccine Booster Dose Protection: A Nationwide Study from Israel

Preprint posted August 27, 2021

<https://t.co/kSl7XcDoKz?amp=1>

There were 1,186,780 Israeli residents aged 60 and older who had been fully vaccinated at least five months prior (became fully vaccinated before March 1, 2021), and were still alive on July 30, 2021 who were eligible. A total of 1,144,690 individuals met the inclusion criteria for the analysis. The data included vaccination dates (first, second and third doses), PCR tests (dates and results), COVID-19 hospitalization date (if relevant), demographic variables such as age, gender, and demographic group (General Jewish, Arab, ultra-Orthodox Jewish), and clinical status (mild, severe). Severe disease was

defined as: resting respiratory rate >30 breaths per minute, or oxygen saturation on room air <94%, or ratio of PaO₂ to FiO₂ <300.

They considered 12 days as the time it took the booster dose to affect the observed number of confirmed infections. The study period started at the beginning of the booster vaccination campaign on July 30, 2021. The end date was chosen as August 22, 2021, to minimize the effects of missing outcome data due to delays in the reporting of test results. Choosing 12 days following booster vaccination as the cutoff is scientifically justified from an immunological perspective, as studies have shown that following the booster dose, neutralization levels increase only after several days.

To further examine the protection as a function of time from the booster dose, they fitted a Poisson regression comparing the 'booster' and 'no-booster' cohorts as above, while including each day, from day 1 up to day 24 after the booster vaccination, as a separate factor in the model. The period before receiving the booster dose ('no-booster' cohort) was used as the reference category. The follow-up time for this analysis started on July 30, 2021, and ended on August 22, 2021.

Twelve days or more after the booster dose they found an 11.4-fold (95% CI: [10.0, 12.9]) decrease in the relative risk of confirmed infection, and a >10-fold decrease in the relative risk of severe illness. Under a conservative sensitivity analysis, they found ≈5-fold protection against confirmed infection.

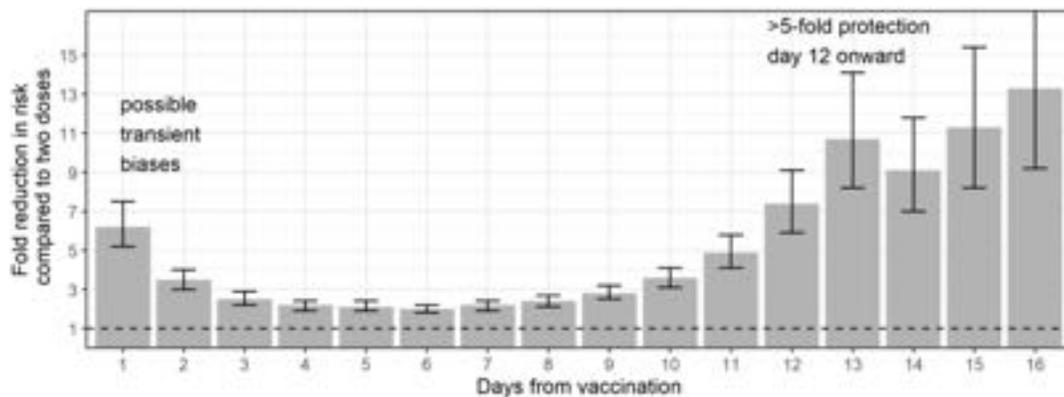


Figure 2. Booster protection against confirmed infection as a function of the number of days following the booster dose. Because of wide confidence intervals, only days 1-16 are shown. Protection is given as a fold reduction in risk relative to people who received only two vaccine doses. Data is based on about 1 million individuals aged 60 or older, who received the 3rd dose boost. The dashed line represents no added protection by the booster dose.

Comments: Based on this study, in persons over age 60 a booster provided >10-fold reduction of severe disease and ~11% reduction of infection. This brings VE up to over 90%. Based on the Israeli data, in persons over age 60, a booster dose at 6-8 months seems appropriate.

Outbreak Associated with SARS-CoV-2 B.1.617.2 (Delta) Variant in an Elementary School — Marin County, California, May-June 2021
MMWR August 27, 2021

On May 25, 2021, the Marin County Department of Public Health (MCPH) was notified by an elementary school that on May 23, an unvaccinated teacher had reported receiving a positive test result for SARS-CoV-2, the virus that causes COVID-19. The teacher reported becoming symptomatic on May 19 but continued to work for 2 days before receiving a test on May 21. On occasion during this time, the teacher read aloud unmasked to the class despite school requirements to mask while indoors. Beginning May 23, additional cases of COVID-19 were reported among other staff members, students, parents, and siblings connected to the school.

The health department-initiated case investigation and contact tracing included WGS of available specimens. A total of 27 cases were identified, including that of the teacher. During May 23-26, among the teacher's 24 students, 22 students, all ineligible for vaccination because of age, received testing for SARS-CoV-2; 12 received positive test results. The attack rate in the two rows seated closest to the teacher's desk was 80% (eight of 10) and was 28% (four of 14) in the three back rows (Fisher's exact test; $p = 0.036$).

During May 24-June 1, six of 18 students in a separate grade at the school, all also too young for vaccination, received positive SARS-CoV-2 test results. Eight additional cases were also identified, all in parents and siblings of students in these two grades. Among these additional cases, three were in persons fully vaccinated in accordance with CDC recommendations. Among the 27 total cases, 22 (81%) persons reported symptoms; the most frequently reported symptoms were fever (41%), cough (33%), headache (26%), and sore throat (26%). WGS of all 18 available specimens identified the Delta variant.



Comment: This is a remarkable study showing just how transmissible Delta can be. The attack rate in one affected classroom was 50%; risk correlated with seating proximity to the teacher. Vaccines are still moderately effective against mild symptomatic Delta variant [highly effective against severe disease] but breakthrough cases can occur, but transmission risk remains highest among unvaccinated persons in

schools. In addition to vaccination, we still need a layered approach which includes NPI strategies, including masking, hand hygiene, and social distancing to ensure safe school instruction.

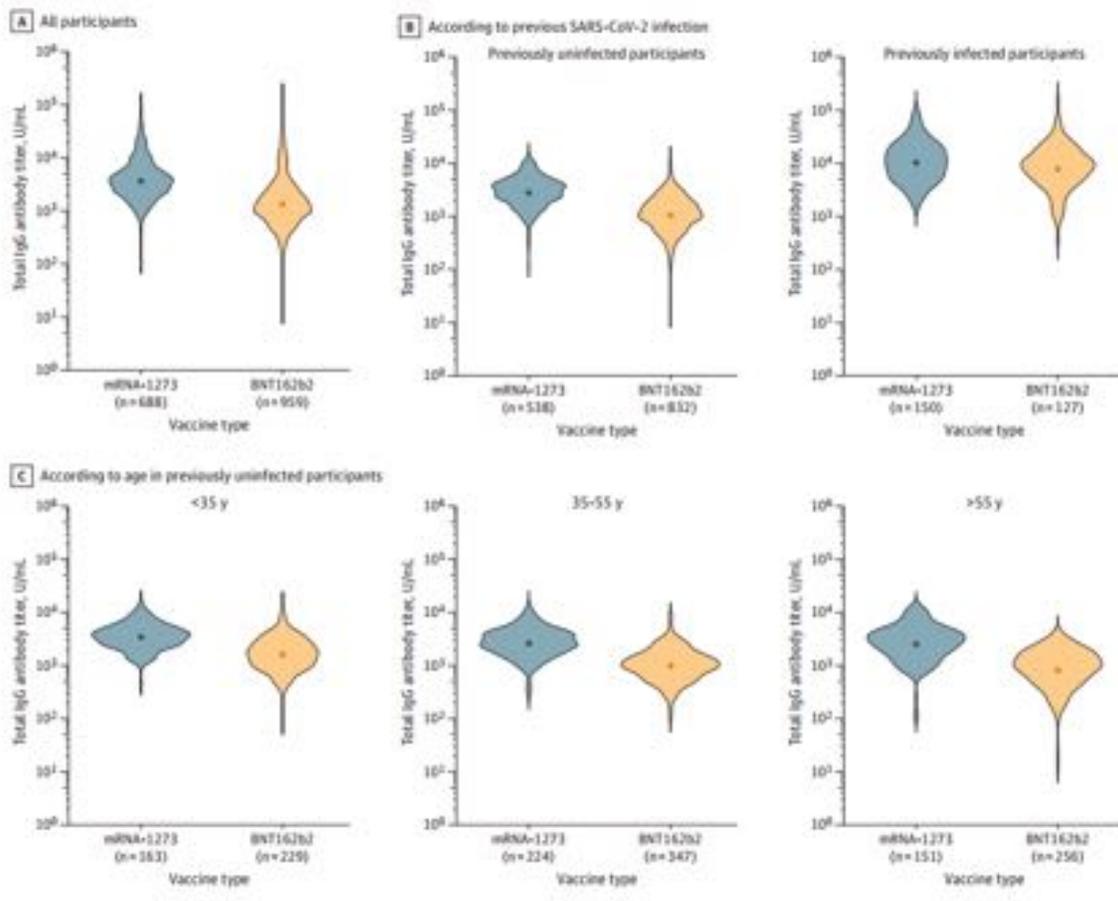
Comparison of SARS-CoV-2 Antibody Response Following Vaccination with BNT162b2 and mRNA-1273

JAMA published online August 30, 2021

doi:10.1001/jama.2021.15125

Healthcare workers at a tertiary care center who were scheduled for vaccination with 2 doses of either Moderna or Pfizer were invited to participate in this prospective cohort. Serologic testing was performed prior to vaccination as well as 6 to 10 weeks after the second dose. Antibody levels to the receptor-binding domain of the SARS-CoV-2 spike protein were measured with an anti-SARS-CoV-2 S enzyme immunoassay.

Higher antibody titers were observed in participants vaccinated with 2 doses of Moderna compared with those vaccinated with Pfizer (geometric mean titer ($P < .001$). Previously infected participants had higher antibody titers compared with previously uninfected participants ($P < .001$). In both groups, those vaccinated with Moderna had higher antibody titers compared with those vaccinated with Pfizer ($P < .001$; previously infected: GMT, 10 708 U/mL [95% CI, 9311-12 315] vs 8174 U/mL [95% CI, 6923-9649]; $P = .01$). The difference in antibody levels according to previous infection was higher than the difference between the 2 mRNA vaccines.



Comment: This study demonstrated a significantly higher humoral immunogenicity of the SARS-CoV-2 Moderna vaccine compared with Pfizer, in infected as well as uninfected participants, and across age categories. The higher mRNA content in Moderna compared with Pfizer and the longer interval between priming and boosting for Moderna (4 weeks vs 3 weeks for Pfizer) might explain this difference. The result of this paper is similar to the recent prepublication study from Mayo Clinic reviewed in the Briefing August 13, 2021. There has been some thought about the interval between the first and second dose in optimizing the response of the second dose. Despite this difference it is still unclear what the exact antibody level is which is protective and the impact of T and B-cell response.